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Association of somatometrics at time of Fontan evaluation with in-hospital and long-term survival outcomes of patients with single ventricle palliation

By

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Degree to be awarded: MPH

Epidemiology

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Bachelor of Science in Public Health

Georgia State University

2021

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

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in Epidemiology

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Abstract

Association of somatometrics at time of Fontan evaluation with in-hospital and long-term survival outcomes of patients with single ventricle palliation

By Jackie Luong

In the United States (US), it is estimated that approximately 2,000 newborns are born each year with single-ventricle (SV) type of congenital heart defect. Survival for SV patients can be improved through a series of palliative procedures which culminate in the Fontan procedure. Growth in children is closely associated to their hemodynamic well-being. However, there is little knowledge of the relationship between height and weight on outcomes of patients with single ventricle physiology. We hypothesize that pre-Fontan somatometrics may be a proxy variable for the hemodynamic efficiency of the single ventricle circulation and a predictor of long-term outcomes for Fontan patients. We assessed the distribution of the somatometrics height-for-age, weight-for-age, and weight-for-height in a large multi-center cohort of patients evaluated for Fontan procedure. We used Kaplan-Meier survival curves and adjusted Cox hazard models with relevant covariates to assess in-hospital and long-term survival outcomes. The study cohort included a total of 1,401 Fontan patients enrolled between 1982 and 2003 in the Pediatric Cardiac Care Consortium, a US based registry for congenital heart interventions. Of them 761 (54.3%) had a systemic left ventricle (LV) phenotype and 640 (45.7%) had a systemic right ventricle (RV) phenotype. The median height at pre-Fontan catheterization was 92.0 cm (Q1-Q3: 85.0, 102.0) and the median weight was 13.3 kg (Q1-Q3: 11.5, 15.5). A total of 75 patients died in hospital after the Fontan procedure, and 1,326 survived to discharge. Over a median follow up period of 18.8 years (IQR: 16.2-22.4) additional 162 deaths occurred. After adjustment for other covariates, in-hospital mortality was associated with low weight tertile, but there was no association between the overall post-discharge survival and the weight z-score. However, stratification analysis revealed a beneficial effect only for patients with systemic LV.

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INTRODUCTION

In the United States (US), it is estimated that approximately 2,000 newborns are born each year with single-ventricle (SV) type of congenital heart defect [1]. The term “single-ventricle” is broad and refers to structural cardiac abnormalities with one functional ventricle due to various anatomic abnormalities that most commonly include missing or underdeveloped ventricles, and atretic, underdeveloped, or misaligned atrioventricular valves. Such cases are typically complicated by variable degrees of hypoxemia and decreased cardiac output with implications for the well-being of all body organs [2]. Survival for SV patients can be improved through a series of palliative procedures which culminate in the Fontan procedure. The Fontan procedure completes the separation of the pulmonary from the systemic venous return where oxygenated blood is pumped to the circulatory system by the single ventricle and deoxygenated blood in venous return passively flows into the pulmonary arteries through a cavopulmonary connection [3]. Although there is no standard weight, height, or age for surgery, most centers proceed when the patient is two to four years old [2].

With this unique physiology and improvements in technology and patient selection, SV patients today can have hope for a 30-year survival >80% [2]. However, the course of growth and age is characterized by a chronic state of low cardiac output and elevated systemic venous pressures. Over time these hemodynamic abnormalities may lead to multiple morbidities (including protein-losing enteropathy and liver fibrosis), delayed somatic growth, and premature mortality [2]. For patients with SV, slow somatic growth has been documented, and hemodynamics may have a negative role in this delayed growth. Small series have shown that procedures leading to improved cardiac output in patients with SV during early childhood are followed by improvement in linear growth [4]. One study has shown that during childhood and adolescence, higher brain natriuretic peptide levels and lower systemic cardiac output were associated with lower growth hormone mediator levels [5] suggesting that interventions aiming to improve the hemodynamics may improve linear growth [6-8]. In addition, a study from the Society of Thoracic Surgeons found that a weight for age z score < -2 was associated with significant morbidity and mortality after the Fontan operation independent of other patient and center characteristics [9]. However, there is no information on whether this relationship can predict survival for long-term outcomes after discharge from the hospital. In addition, given the reported relationship between height and cardiac output, it is possible that a similar relationship may exist between height long-term outcomes in single ventricle patients.

We hypothesize that somatometrics, such as height and weight at the time of the Fontan palliation, may be proxy variables for the hemodynamic efficiency of the single ventricle circulation and a predictor of long-term outcomes for Fontan patients.

METHODS

We used the Pediatric Cardiac Care Consortium (PCCC), a large multicenter US-based clinical registry of pediatric cardiac surgical interventions for infants, children, and adults with congenital heart defects to conduct a retrospective cohort study [10]. Patients were enrolled between 1982 and 2003 at the time of their cardiac catheterization in preparation for the Fontan procedure (pre-Fontan catheterization). Death events were captured prospectively from the registry and by matching with the US National Death Index (NDI).

From this consortium, we screened patients who had undergone Fontan palliation between the ages of 1 and 21 years and had received their first Fontan operation at a PCCC center between the years 1982 and 2003 (although surgery can occur at an age range of three to four years or later, and therefore, surgeries may occur up until year 2011). Inclusion criteria consisted of patients who had a single ventricle, had undergone the Glenn surgical procedure, had pre-Fontan cardiac catheterization within one year of the Fontan operation, and had complete surgical data. Exclusion criteria consisted of patients with chromosomal abnormalities, an atrial-pulmonary connection (AP Fontan), an unclassifiable ventricle, a Fontan outside of the PCCC, surgery outside of the US, surgery post-HIPAA (rule of 2003 that previously allowed direct patient identifiers in national registries), and their age at first Fontan at 21 years or older.

Along with these criteria, we examined descriptive statistics of somatometrics (height, weight and weight-for-height including their age-adjusted values expressed as z-scores in comparison to the general population) at the time of the cardiac catheterization prior to the Fontan procedure, underlying patient diagnosis, type and dates of cardiac procedures, type of dominant ventricle (left or right ventricle), age at Fontan (<2, 2-4, and >4 years), sex at birth, and era of operation (divided by tertiles in 3 eras: 1982-1998, 1999-2002, 2003-2011). Quantitative variables were described by the median with the interquartile range.

Pre-Fontan catheterization height and weight values were converted to z-scores through the Centers for Disease Control and Prevention (CDC) growth charts (year 2000) for ages zero to <21 years. We assessed whether exposures of height-for-age (height z-score) and weight-for-age (weight z-score) were associated with long-term survival outcomes post-Fontan operation discharge after adjustment for other covariates known to affect Fontan outcomes. To examine height, weight, and weight-for-height distribution, we used a histogram to test for normality. To assess survival, we used unadjusted Kaplan-Meier Curves and adjusted Cox hazard models with relevant covariates for short and long follow-up times. Kaplan-Meier curves were given for exposures of interest and exposures stratified by dominant ventricle type. Short-term follow-up time was defined as mortality in the hospital following the Fontan procedure and before patient discharge. Long-term follow-up time was defined as the time from the date of hospital discharge until post-discharge mortality events up to December 31, 2021, whichever occurred first. Three Cox hazard models were conducted with the first model using height z-score as the exposure, the second the weight z-score and the third the weight-for-height z-score. Height, weight, and weight-for-height z-scores were categorized in tertiles as low, middle, and high. Covariates included in the multivariable model included sex, type of dominant ventricle, age at Fontan, and the era of operation. Being of male sex, having a dominant right ventricle, having the Fontan operation at an older age than 4 years, and operating in an earlier era are associated with worse outcomes. Analysis was conducted using SAS (version 9.4; SAS Institute, Gary, NC). Statistical significance was categorized by a p-value threshold of 0.05 and 95% confidence intervals (CI).

RESULTS

A total of 1,401 patients met inclusion criteria from the initial 3,284 patients with a Fontan procedure in the PCCC (Figure 1). For the Kaplan-Meier curves and survival analysis, the final cohort size was 1,001 for height z-score and 1,381 for weight z-score. Height z-scores were categorized at the 33% percentile of -1.25714 and 66% percentile of -0.19660. Weight z-scores were categorized at the 33% percentile of -1.33609 and 66% percentile of -0.29933. Weight-for-height z-scores were categorized at the 33% percentile of -1.00744 and 66% percentile of 0.091247.

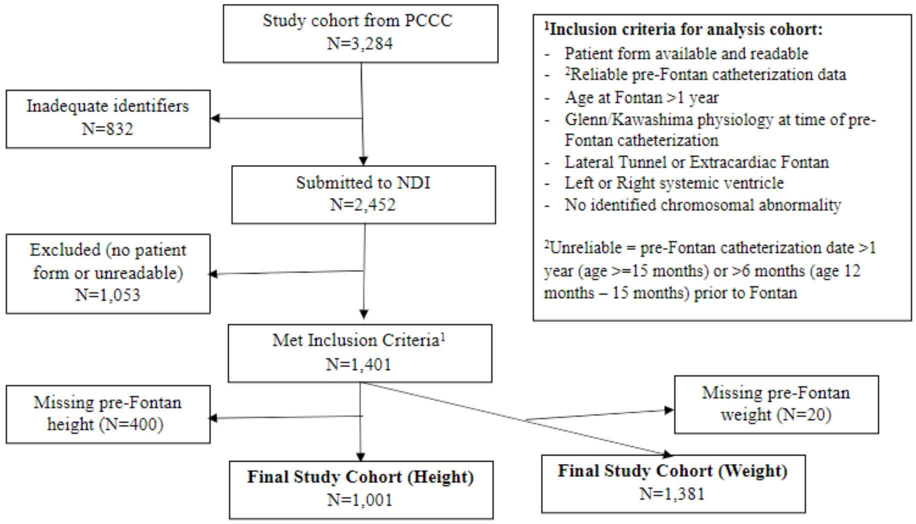


Figure 1. Flowchart depicting exclusion and inclusion criteria.

In the final cohort meeting inclusion criteria, 62.1% were male. The median age at first Fontan was 3.1 years (Q1-Q3: 2.4, 4.3). For type of diagnosis, 32.5% had a hypoplastic right heart (HRH) followed by 21.6% with a hypoplastic left heart (HLH) and 17.2% having another single ventricle diagnosis. When comparing dominant ventricle type, 54.3% had a left ventricle (LV). The median height at pre-Fontan catheterization was 92.0 centimeters (Q1-Q3: 85.0, 102.0) and the median weight was 13.3 kilograms (Q1-Q3: 11.5, 15.5) (Table 1).

Table 1. Demographics of Fontan Cohort

Characteristic	**Sample (n) (%)**	**Median (Q1, Q3)**
Sex		
Male	870 (62.1)	
Female	531 (37.9)	
Age at Fontan (years)		3.1 (2.4, 4.3)
Diagnosis		
Complex Transposition	101 (7.2)	
Double Outlet Right Ventricle (DORV)	128 (9.1)	
Hypoplastic Left Heart (HLH)	303 (21.6)	
Hypoplastic Right Heart	455 (32.5)	
Single Ventricle (SV) (other)	241 (17.2)	
Straddling	1 (0.1)	

Tetralogy of Fallot (TOF)/Pulmonary Atresia (PA)/Ventricular Septal Defect (VSD)	2 (0.1)	
Unbalances Complete Atrio-Ventricular Canal (UCAV)	170 (12.1)	
Height at pre-Fontan catheterization (centimeters), n=1,001		92.0 (85.0, 102.0)
Weight at pre-Fontan catheterization (kilograms), n=1,381		13.3 (11.5, 15.5)
Weight-for-Height (%), n=915		32.1 (8.7, 65.6)
Ventricle Type		
Left ventricle (LV)	761 (54.3)	
Right ventricle (RV)	640 (45.7)	

The distribution of height, weight, and weight-for-height z-scores were left-skewed (Figures 2-4). For each somatometric variable, over half of the sample was below the mean values of the general population.

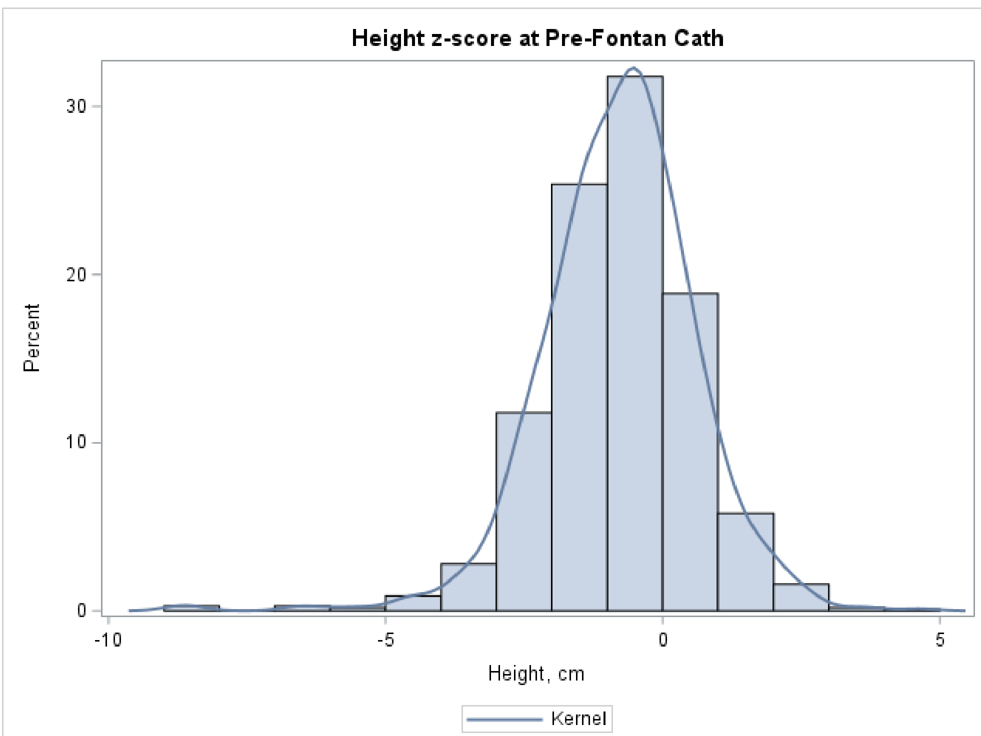


Figure 2. Histogram of height-for-age z-scores (normality p-value <0.001, skewness = -0.70, kurtosis = 3.62)

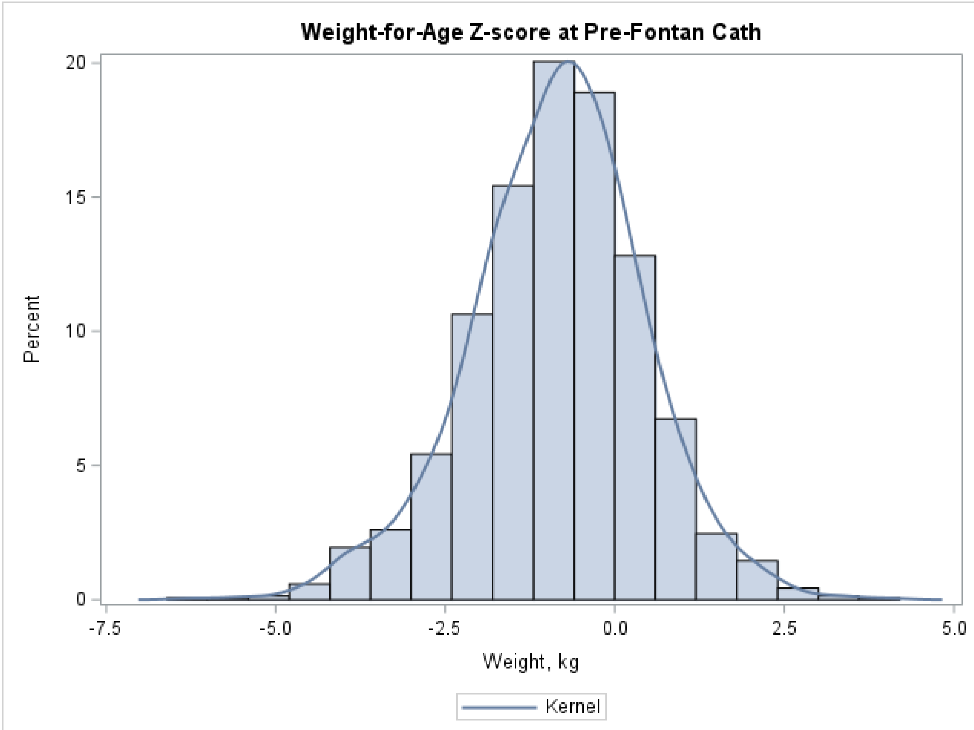


Figure 3. Histogram of weight-for-age z-scores (normality p-value <0.001, skewness = -0.19, kurtosis = 0.38)

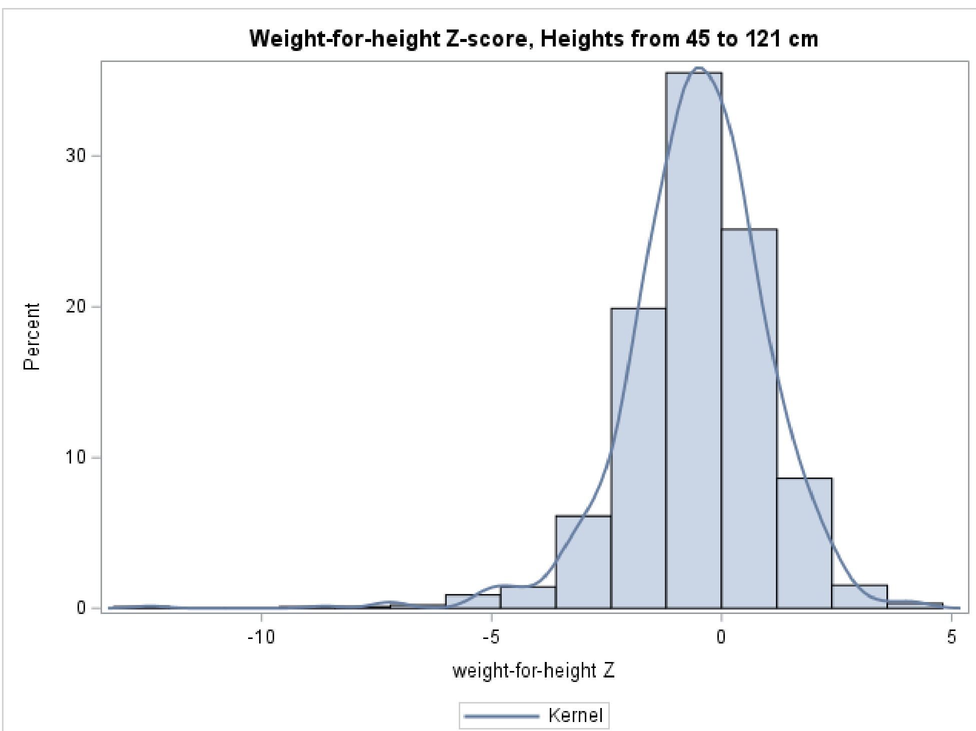


Figure 4. Weight-for-height z-score histogram plot (normality p-value <0.001, skewness = -1.05, kurtosis = 5.57)

When analyzing the short-term outcomes (in-hospital mortality) there were 57 events out of 1,001 patients (5.7%) among the height and weight-for-height exposure and 73 out of 1,381 (5.3%) among those included in the weight exposure. Among short-term outcomes, the adjusted odds of mortality among the middle height z-scores was 0.80 times the corresponding odds among the lowest height tertiles (95% CI: 0.40, 1.55). The adjusted odds of mortality among the highest values of height tertiles was 1.16 times the corresponding odds among the lowest height tertiles (95% CI: 0.61, 2.20). The adjusted odds of short-term outcomes among the middle weight tertiles was 0.87 times the corresponding odds among the lowest weight tertiles (95% CI: 0.50, 1.49). The adjusted odds of mortality among the highest values of weight tertiles was 0.51 times the corresponding odds among the lowest weight tertiles (95% CI: 0.27, 0.97) (Table 2).

Table 2. In-hospital survival analysis after Fontan

	Univariable Analysis				**Multivariable Analysis**			
	OR	**95% CI**		**P-Value**	**OR**	**95% CI**		**P-Value**
Height-for-age Z-score								
Low	Ref				Ref			
Middle	0.79	0.40	1.55	0.49	0.80	0.40	1.59	0.52
High	1.14	0.60	2.14	0.69	1.16	0.61	2.20	0.65
Age at Fontan								
<2 years	Ref				Ref			
2-4 years	0.29	0.16	0.52	<0.001	0.30	0.15	0.6	<0.001
>4 years	0.35	0.18	0.67	0.001	0.35	0.16	0.75	0.01
Sex								
Male	Ref				Ref			
Female	0.62	0.37	1.04	0.07	0.68	0.38	1.23	0.20
Dominant Ventricle								
Right ventricle	Ref				Ref			
Left ventricle	0.81	0.51	1.29	0.37	0.68	0.39	1.18	0.17
Era								
1982-1998	Ref							
1999-2002	0.55	0.31	0.98	0.04	0.72	0.37	1.40	0.33
2003-2011	0.61	0.34	1.07	0.09	0.69	0.35	1.35	0.28

	Univariable Analysis				Multivariable Analysis			
	OR	95% CI		P-Value	OR	95% CI		P-Value
Weight-for-age Z-score								
Low	Ref				Ref			
Middle	0.86	0.51	1.47	0.59	0.87	0.50	1.49	0.60
High	0.47	0.25	0.88	0.02	0.51	0.27	0.97	0.04
Age at Fontan								
<2 years	Ref				Ref			
2-4 years	0.29	0.16	0.52	<0.001	0.33	0.18	0.61	<0.001
>4 years	0.35	0.18	0.67	0.001	0.39	0.20	0.77	0.006
Sex								
Male	Ref				Ref			
Female	0.62	0.37	1.04	0.07	0.63	0.37	1.07	0.09
Dominant Ventricle								
Right ventricle	Ref				Ref			
Left ventricle	0.81	0.51	1.29	0.37	0.83	0.51	1.35	0.44
Era								
1982-1998	Ref				Ref			
1999-2002	0.55	0.31	0.98	0.04	0.59	0.33	1.06	0.08
2003-2011	0.61	0.34	1.07	0.09	0.73	0.40	1.33	0.31

	Univariable Analysis				Multivariable Analysis			
	OR	95% CI		P-Value	OR	95% CI		P-Value
Weight-for-Height Z-score								
Low	Ref				Ref			
Middle	0.53	0.25	1.13	0.10	0.54	0.25	1.16	0.11
High	0.84	0.43	0.25	0.62	0.80	0.40	1.58	0.52
Age at Fontan								
<2 years	Ref				Ref			
2-4 years	0.29	0.16	0.52	<0.001	0.30	0.15	0.61	<0.01
>4 years	0.35	0.18	0.67	0.001	0.20	0.08	0.52	<0.01
Sex								
Male	Ref				Ref			
Female	0.62	0.37	1.04	0.07	0.69	0.36	1.32	0.26
Dominant Ventricle								
Right ventricle	Ref				Ref			
Left ventricle	0.81	0.51	1.29	0.37	0.75	0.41	1.37	0.34
Era								

1982-1998	Ref				Ref			
1999-2002	0.55	0.31	0.98	0.04	0.60	0.29	1.27	0.18
2003-2011	0.61	0.34	1.07	0.09	0.75	0.36	1.55	0.43

Table 2. Multivariable and univariable logistic regression of height, weight, and weight-for-height exposures on short-term outcomes (adjusted for age at Fontan, sex, dominant ventricle type, and era of operation).

For the exposure of height z-score in long-term outcomes, the mean follow-up time was 22.7 years (standard deviation = 0.28). Among the lowest tertile (indicated by a 0 in Figure 5) there were 47 outcomes (294 censored). In the middle tertile (indicated by 1) there were 34 outcomes (308 censored) and in the highest tertile (indicated by 2) there were 35 outcomes (283 censored). For the exposure of weight z-score, the mean follow-up time was 22.1 years (standard deviation= 0.22). Among the lowest tertiles (indicated by a 0 in Figure 6) there were 60 outcomes (401 censored). In the middle tertiles (indicated by 1) there were 48 outcomes (413 censored) and in the highest tertiles (indicated by 2) there were 49 outcomes (410 censored). Overall, there was not a statistically significant difference in mortality between the different levels of tertiles for height (p-value = 0.27) and weight (p-value = 0.37). However, when stratified by dominant ventricle type (as this cohort is defined by single-ventricle congenital heart defects), height z-scores (p-value = 0.02) and weight z-scores (p-value = 0.04) were associated with mortality among those with a left ventricle type. A dominant right ventricle type was not associated with differences in long-term outcomes in z-scores in height, weight, and weight-for-height.

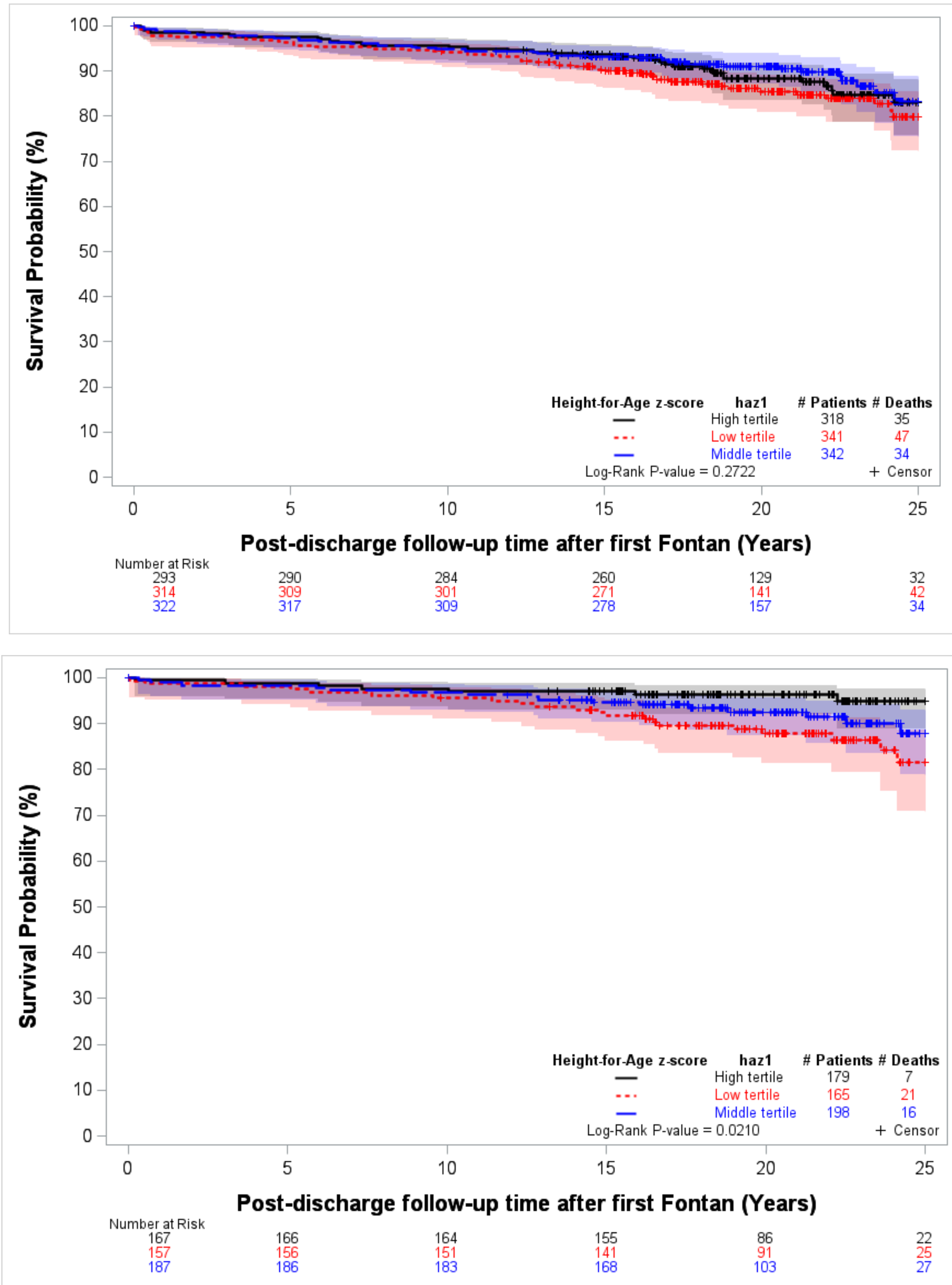
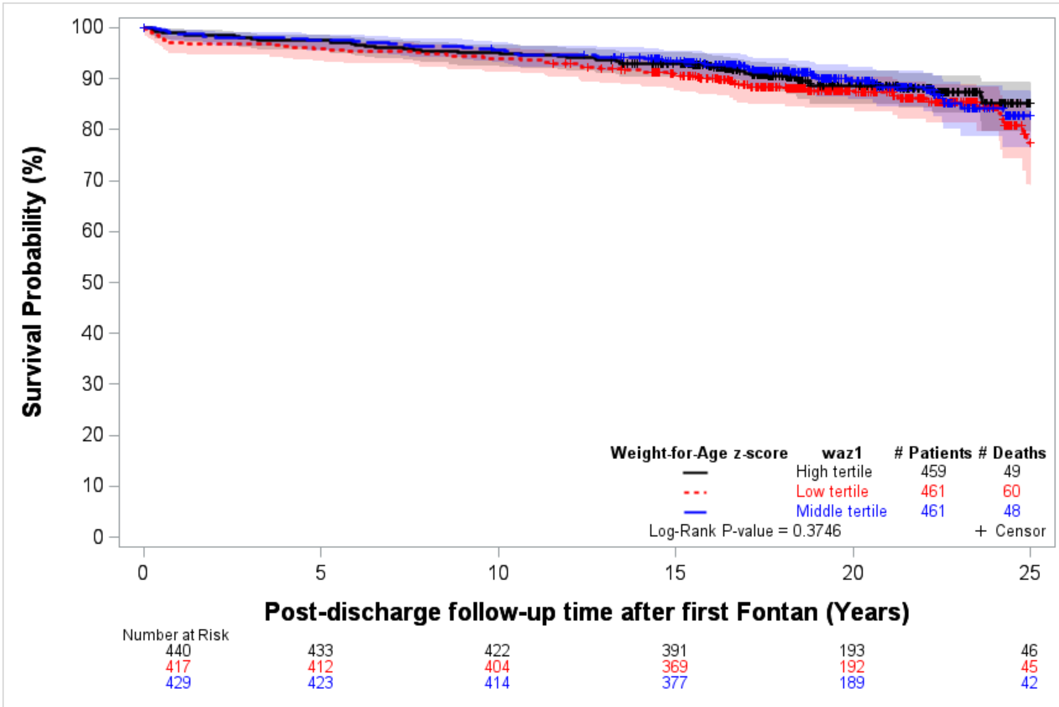


Figure 5. Kaplan-Meier plots of height-for-age z-scores overall (first) and height-for-age z-scores among those with a left dominant ventricle (second).



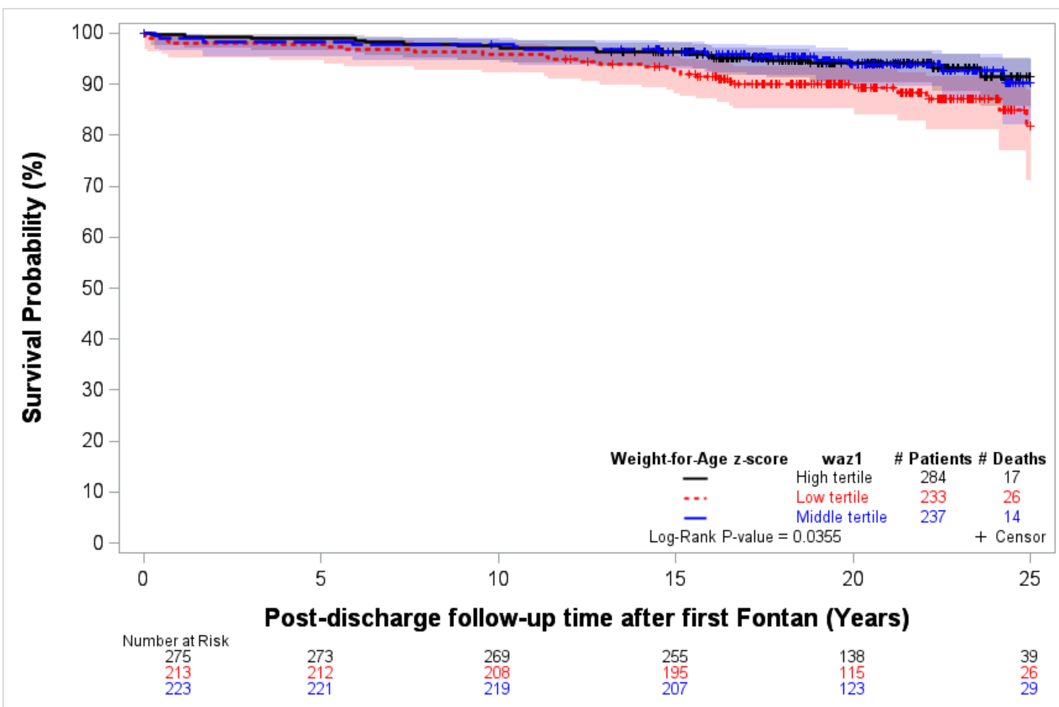


Figure 6. Kaplan-Meier plots of weight-for-age z-scores overall (first) and weight-for-age z-scores among those with a left dominant ventricle (second).

The adjusted hazard of long-term mortality among the middle height tertiles was 0.79 times the corresponding hazard among the lowest height tertiles (95% CI: 0.51, 1.24). The adjusted hazard of mortality among the highest height tertile was 0.86 times the corresponding hazard among the lowest height tertiles (95% CI: 0.55, 1.33).

The adjusted hazard of long-term mortality among the middle weight tertile was 0.84 times the corresponding hazard among the lowest weight tertile (95% CI: 0.58, 1.23). The adjusted hazard of mortality among the highest weight tertile was 0.90 times the corresponding hazard among the lowest weight tertile (95% CI: 0.62, 1.32).

Table 3. Long-term survival analysis at Fontan post-discharge

	Univariable Analysis				**Multivariable Analysis**			
	HR	**95% CI**		**P-Value**	**HR**	**95% CI**		**P-Value**
Height-for-age Z-score								
Low	Ref				Ref			
Middle	0.71	0.45	1.10	0.12	0.79	0.51	1.24	0.30
High	0.80	0.51	1.23	0.30	0.86	0.55	1.33	0.50
Age at Fontan								
<2 years	Ref				Ref			
2-4 years	1.84	0.93	3.65	0.08	1.86	0.80	4.32	0.15
>4 years	2.53	1.26	5.10	0.01	2.49	1.06	5.86	0.04
Sex								
Male	Ref				Ref			
Female	0.87	0.63	1.20	0.41	0.73	0.49	1.08	0.12
Dominant Ventricle								
Left	Ref				Ref			
Right	0.40	0.29	0.55	<0.001	0.45	0.31	0.66	<0.001
Era								
1982-1998	Ref				Ref			
1999-2002	0.73	0.49	1.09	0.12	0.85	0.52	1.37	0.50
2003-2011	1.07	0.71	1.61	0.76	1.07	0.66	1.76	0.78

	Univariable Analysis				**Multivariable Analysis**			
	HR	**95% CI**		**P-Value**	**HR**	**95% CI**		**P-Value**
Weight-for-age Z-score								
Low	Ref				Ref			
Middle	0.81	0.56	1.81	0.27	0.84	0.58	1.23	0.37
High	0.84	0.58	1.21	0.35	0.90	0.62	1.32	0.60

Age at Fontan								
<2 years	Ref				Ref			
2-4 years	1.84	0.93	3.65	0.08	1.88	0.94	3.76	0.07
>4 years	2.53	1.26	5.10	0.01	2.54	1.25	5.14	0.01
Sex								
Male	Ref				Ref			
Female	0.87	0.63	1.20	0.41	0.89	0.64	1.24	0.49
Dominant Ventricle								
Left	Ref				Ref			
Right	0.40	0.29	0.55	<0.001	0.39	0.28	0.55	<0.001
Era								
1982-1998	Ref				Ref			
1999-2002	0.73	0.49	1.09	0.12	0.68	0.45	1.01	0.06
2003-2011	1.07	0.71	1.61	0.76	0.83	0.54	1.27	0.39
	Univariable Analysis				**Multivariable Analysis**			
	HR	**95% CI**		**P-Value**	**HR**	**95% CI**		**P-Value**
Weight-for-Height Z-score								
Low	Ref				Ref			
Middle	1.05	0.64	1.71	0.85	1.06	0.65	1.74	0.81
High	1.14	0.70	1.85	0.59	1.28	0.79	2.08	0.32
Age at Fontan								
<2 years	Ref				Ref			
2-4 years	1.84	0.93	3.65	0.08	1.87	0.81	4.36	0.14
>4 years	2.53	1.26	5.10	0.01	2.12	0.87	5.13	0.10
Sex								
Male	Ref				Ref			
Female	0.87	0.63	1.20	0.41	0.65	0.42	1.01	0.06
Dominant Ventricle								
Left	Ref				Ref			
Right	0.40	0.29	0.55	<0.001	0.43	0.29	0.66	<0.01
Era								
1982-1998	Ref				Ref			
1999-2002	0.73	0.49	1.09	0.12	0.89	0.53	1.50	0.66
2003-2011	1.07	0.71	1.61	0.76	1.25	0.74	2.13	0.41

Table 3. Multivariable and univariable Cox proportional hazards model of long-term outcomes for height, weight, and weight-for-height exposures (adjusted for age at Fontan, sex, dominant ventricle type, and era of operation).

DISCUSSION

This analysis demonstrated consistent findings of height and weight deficits at the time of the Fontan procedure. For each distribution, more than half of patients were below normal height-for-age and weight-for-age at pre-Fontan catheterization. This growth deficit may be explained by the strain of the single ventricle features.

Consistent with previous studies [8], we found that top tertile weight at Fontan is a predictor of in-hospital survival, but not for long-term survival in the overall cohort. However, when stratifying by ventricle type, left dominant ventricle was associated with significantly worse outcomes among the group with lowest value z-scores. For height-for-age and weight-for-age z-scores, there was no difference between low, middle, and high tertiles in short-term outcomes (in-hospital deaths) in both univariable and multivariable analyses.

This analysis is subject to certain limitations. There were many missing height observations (28.5% missing), where those with missing height may be statistically different than those with available measurements in outcome measures. Nonetheless, this study has certain strengths in that the cohort is generalizable to populations with a single ventricle and contains the ability to follow patients throughout large periods of growth such as puberty [7]. For future studies, discrete increases in z-score of height, weight, and weight-for-height of one standard deviation and changes in hazard of longitudinal death may be examined. We could also examine the weight of the patients that were missing height and see whether if they are distributed differently than the remaining cohort.

Overall, somatometrics at pre-Fontan catheterization were not significantly associated with long-term survival. However, although insignificant, those with larger measurements had better outcomes than those with smaller measurements. In conclusion, among newborns with a left dominant ventricle, those with smaller height and weight measurements compared to the general population have significantly worse long-term survival than those with larger measurements.

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